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Interleukin-17A: a unique pathway in immune-mediated diseases: psoriasis, psoriatic arthritis and rheumatoid arthritis

Bruce W. Kirkham,[1] Arthur Kavanaugh[2] and Kristian Reich[3]

[1]*Department of Rheumatology, Guy's & St Thomas' NHS Foundation Trust, London, UK,* [2]*Division of Rheumatology, Allergy and Immunology, University of California, San Diego, CA, USA, and* [3]*Dermatologikum Hamburg, Hamburg, Germany*

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Correspondence: Bruce W. Kirkham, Department of Rheumatology, Guy's & St Thomas' NHS Foundation Trust, 4th Floor Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK.
Email: bruce.kirkham@gstt.nhs.uk
Senior author: Bruce W. Kirkham

Summary

Experimental evidence points to the importance of the cytokine interleukin-17A (IL-17A) in the pathogenesis of several immunoinflammatory diseases including psoriasis, psoriatic arthritis and rheumatoid arthritis. Although a principal effector of T helper type 17 cells, IL-17A is produced by many other cell types including $CD8^+$ T cells and $\gamma\delta$ T cells, and is found at high levels associated with mast cells and neutrophils at sites of skin and joint disease in humans. IL-17A up-regulates expression of numerous inflammation-related genes in target cells such as keratinocytes and fibroblasts, leading to increased production of chemokines, cytokines, antimicrobial peptides and other mediators that contribute to clinical disease features. Importantly, IL-17A must be considered within the context of the local microenvironment, because it acts synergistically or additively with other pro-inflammatory cytokines, including tumour necrosis factor. Several direct IL-17A inhibitors have shown promising activity in proof of concept and phase 2 clinical studies, thereby providing confirmation of experimental data supporting IL-17A in disease pathogenesis, although levels of response are not predicted by pre-clinical findings. IL-17A inhibitors produced rapid down-regulation of the psoriasis gene signature and high clinical response rates in patients with moderate-to-severe plaque psoriasis, consistent with an important role for IL-17A in psoriasis pathogenesis. Clinical response rates with IL-17A inhibitors in psoriatic arthritis and rheumatoid arthritis, however, were improved to a lesser degree compared with placebo, suggesting that IL-17A is either important in a subset of patients or plays a relatively minor role in inflammatory joint disease. Ongoing phase 3 clinical trials should provide further information on the role of IL-17A in these diseases.

Keywords: biological therapy; interleukin-17A; psoriasis; psoriatic arthritis; rheumatoid arthritis.

Introduction

The discovery of T helper type 17 (Th17) cells in 2005 was an important advance in understanding the pathogenesis of immune-mediated inflammatory diseases.[1–3] In addition to identification of an important source of the cytokine interleukin-17A (IL-17A), a principal effector of Th17 cells, it also explained and substantiated the already known important roles of IL-17A in experimental models of immunoinflammatory diseases.[4–6] Interleukin-17A is postulated to play roles in human disease pathogenesis based on the presence of this cytokine in skin and/or joints of patients with immune-mediated diseases such as psoriasis, rheumatoid arthritis (RA) and psoriatic arthritis (PsA).[7–10] These observations provided the rationale for development of biological agents targeting IL-17A signalling pathways, and today, IL-17A pathway inhibitors are both therapeutic candidates as well as tools for dissecting out the role of IL-17 signalling in human disease pathogenesis. We summarize here current experimental findings implicating the IL-17 pathway in the pathogenesis of psoriasis, PsA and RA, which underlie the rationale for

recent clinical trials using IL-17 pathway inhibitors. Comparisons between pre-clinical and clinical findings may enhance our understanding of the differences in IL-17A-mediated pathogenesis across experimental platforms and human diseases as well as highlight potential benefits and drawbacks with these new therapies.

IL-17 and IL-17 receptor families

Interleukin-17A is one member of a cytokine family comprised of five other members, namely IL-17B through IL-17F, which have varying homology with IL-17A ranging from 50% for IL-17F to 16% for IL-17E.[11,12] Both IL-17A and IL-17F are secreted by Th17 cells and other immune cells, including innate lymphoid cells,[13] as disulphide-linked homodimers but can also form IL-17A/IL-17F heterodimers (Fig. 1). Interleukin-17A is about 10–30-fold more potent than IL-17F, whereas the IL-17A/IL-17F heterodimer has intermediate activity.[12]

The IL-17 receptor family comprises five subunits termed Interleukin-17A receptor (IL-17RA) through IL-17RE, with conserved structural features including an extracellular fibronectin III-like domain a single transmembrane domain and a cytoplasmic SEF/IL-17R (SEFIR) domain (Fig. 1).[12] IL-17A, IL-17A/F and IL-17F bind to a receptor complex consisting of two IL-17RA chains and one IL-17RC subunit. IL-17RA and IL-17RC interact, via SEFIR domains, with the adaptor protein

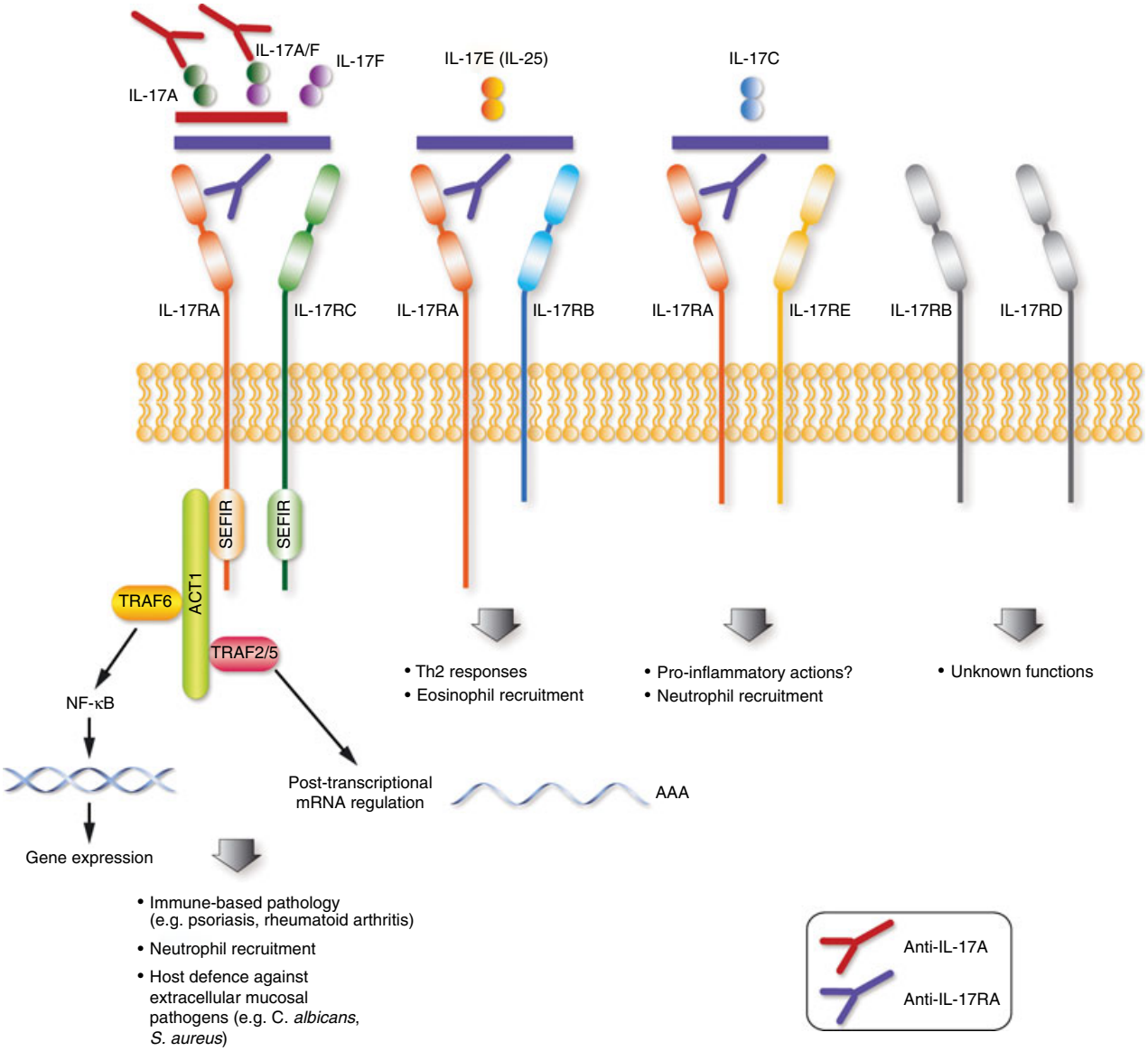

Figure 1. Interleukin-17 (IL-17) and IL-17 receptor family members and their biological roles. Intracellular signalling pathways of IL-17R and targets of IL-17 pathway inhibitors.[12,14–16] Bars (according to colour code) define cytokine functional inhibition by antibody.

Act1, which contains two tumour necrosis factor (TNF) receptor-associated factor (TRAF) -binding motifs.[14] The pathway involving TRAF6 leads to activation of the canonical nuclear factor-κB (NF-κB) and mitogen-activated protein kinase pathways, and the CCAAT/enhancer binding protein (C/EBP) transcription factors resulting in pro-inflammatory gene expression.[17] A TRAF6-independent, TRAF2/5 signalling complex associated with IL-17Rs has also been identified that results in enhanced mRNA stability for the chemokine CXCL1.[18,19] Disruption of the relative balance of these two signalling pathways has been hypothesized to underlie autoimmune pathogenesis in certain cases.[14]

In rheumatoid synoviocytes, IL-17A and IL-17F stimulated downstream signalling in a similar but not identical manner, with IL-17A regulating a much larger number of inflammation-related genes compared with IL-17F.[20] These differences suggest that IL-17A and IL-17F have overlapping but distinct functions. Interleukin-17 receptors are detected on a wide variety of immune and connective tissue cells including monocytes/macrophages, dendritic cells, neutrophils, keratinocytes, mast cells, epithelial cells and vascular endothelial cells. Although not all IL-17 receptors have been identified as functional, their wide distribution suggests that IL-17A affects many cell types, including establishment of autocrine feedback loops in cells producing IL-17A.

Three biological agents that block IL-17A signalling are currently in clinical development and have advanced to phase 3 trials: secukinumab (AIN457), ixekizumab (LY2439821) and brodalumab (AMG-827) (Table 1). Secukinumab is a fully human IgG1κ anti-IL-17A monoclonal antibody[21]; ixekizumab is a humanized IgG4 anti-IL-17A monoclonal antibody[22]; and brodalumab is a fully human anti-IL-17RA monoclonal antibody.[23] The former two neutralize IL-17A, whereas the latter blocks IL-17 family members that act via IL-17RA subunit-containing receptors, including IL-17A, IL-17A/F, IL-17F, IL-17C and IL-17E (Fig. 1). Other IL-17A blocking agents are in earlier stages of development (Table 1).

IL-17A in psoriasis

Experimental evidence

T helper type 17 cells, as well as other cell types, produce IL-17A at immunoinflammatory sites in skin. Numbers of IL-17A-positive cells are increased in lesional skin, of which the vast majority are T cells and neutrophils.[24] $CD8^+$ T cells, and particularly mast cells and neutrophils, stain positively for IL-17A in psoriatic lesions; mast cells are usually enriched in the papillary dermis, neutrophils in epidermal microabscesses and $CD8^+$ T cells in the epidermis.[25,26] Levels of IL-17A, IL-17C and IL-17F mRNA are significantly up-regulated in lesional versus non-lesional skin, whereas levels of IL-17B and IL-17D mRNA are decreased.[27] Importantly, cutaneous IL-17A mRNA levels correlate with disease activity.[28] That IL-17A plays a key role in psoriasis pathogenesis is further supported by evidence that clinical responses to various therapies depend on IL-17 down-regulation in lesional skin.[29–31]

Interleukin-17A acts on multiple cell types relevant to psoriasis pathogenesis. IL-17A is particularly important in driving epidermal pathology by enhancing keratinocyte chemokine expression, including CCL20 (which mediates recruitment of Th17 and dendritic cells to skin), and CXCL1, 3, 5, 6 and 8 (which drive neutrophil recruitment).[9,32] Interleukin-17A also increases expression of antimicrobial peptides including β-defensins and S100A family members,[32,33] and decreases expression of cell adhesion factors, leading to disruption of the skin barrier.[34] Effects of IL-17A overlap with those of other cytokines present in psoriatic lesions and other inflammatory sites. Therefore, effects of IL-17A are likely to depend on the local cytokine milieu, and are augmented through overlapping inflammatory circuits. For example, in primary keratinocytes IL-17A and TNF synergistically up-regulated 160 genes and produced at least additive up-regulation of an additional 196 genes.[35] The synergistically regulated genes were highly correlated with the psoriasis gene signature including genes encoding antimicrobial peptides (S100A7

Table 1. Agents targeting interleukin-17A (IL-17A) or its receptor

		Clinical status[a]			
Agent	Mechanism	Psoriasis	Rheumatoid arthritis	Psoriatic arthritis	Other indications
Secukinumab	Anti-IL-17A	Phase 3	Phase 3	Phase 3	Ankylosing spondylitis (phase 3); asthma (phase 2)
Ixekizumab	Anti-IL-17A	Phase 3	Phase 2[b]	Phase 3	None
Brodalumab	Anti-IL-17RA	Phase 3	Withdrawn	Phase 2	Asthma (phase 2)
SCH 900117	Anti-IL-17A		Phase 1		
ABT-122	Anti-IL-17A/TNF		Phase 1		
RG7624	Anti-IL-17A/IL-17F				Autoimmune disease (phase 1)

[a]Based on ongoing clinical trials according to clinicaltrials.gov on 7 June 2013.
[b]Phase 2 study completed; no clinical trials in RA are ongoing.

and β-defensin-2), chemokines (CCL20, CXCL1 and CXCL8), and the IL-23 p19 subunit.

Clinical findings

Interleukin-17 pathway inhibitors have shown promising activity in early clinical trials in patients with moderate-to-severe psoriasis. Proof of concept for this approach was shown in a single-dose study with secukinumab.[21] At 3 mg/kg intravenously (i.v.), secukinumab significantly reduced mean Psoriasis Area and Severity Index (PASI) scores compared with placebo (58% versus 4%; $P = 0{\cdot}0001$) and allowed more patients to achieve categorical reductions in the investigator's global assessment (IGA; 83% versus 11%; $P = 0{\cdot}0004$) at the week 4 primary end-point. Lesional skin subjected to reverse transcription-PCR and microarray analyses revealed that secukinumab down-regulated expression of multiple chemokines, cytokines and proteins involved in immunoinflammatory responses, particularly IL-12B (shared p40 subunit of IL-12 and IL-23), IL-17A, IL-17F, IL-21, IL-22 (Th17 effector cytokines), CCL20, β-defensin-4 and keratin 16 (marker of activated keratinocytes).

Secukinumab was subsequently evaluated in dose-ranging and regimen-finding, randomized, placebo-controlled phase 2 trials (Table 2). In the dose-ranging study, secukinumab was administered at doses of 25, 75 or 150 mg subcutaneously (s.c.) at baseline and weeks 4 and 8, and

Table 2. Induction therapy with interleukin-17A inhibitors in moderate-to-severe psoriasis in randomized controlled trials

Study	Drug	Baseline PASI	PASI 75 (%)	PGA 0/1 (%)	Mean change in DLQI [DLQI 0, %]	Incidence of infection/serious infection (%)
Leonardi, 2012[a] (Phase 2)[22]	Ixekizumab 10 mg ($n = 28$)	19·2	28·6	25·0	NR	26/0
	Ixekizumab 25 mg ($n = 30$)	18·6	76·7§	70§	–7·1§	43/0
	Ixekizumab 75 mg ($n = 30$)	17·2	82·8§	72§	–8·5§	31/0
	Ixekizumab 150 mg ($n = 28$)	17·7	82·1§	71§	–7·8§	29/0
	Placebo ($n = 27$)	16·5	7·7	8	–2·4	26/0
Papp, 2012[b] (Phase 2)[23]	Brodalumab 70 mg ($n = 39$)	18·8	33§	26†	–6†	Infection incidence not reported: NP (8% versus 8%) and URTI (8% versus 5%) from combined brodalumab versus placebo
	Brodalumab 140 mg ($n = 39$)	19·4	77§	85§	–9§	
	Brodalumab 210 mg ($n = 40$)	20·6	83§	80§	–9§	
	Brodalumab 280 mg[b] ($n = 42$)	17·9	67§	69§	–7§	
	Placebo ($n = 38$)	18·9	0	3	–3	
Papp, 2013[c] (Phase 2)[36]	Secukinumab 25 mg ($n = 29$)	21·6	3	0	NR	Infection incidence: 41%; one patient in 25-mg group had serious infection; no opportunistic infections
	Secukinumab 25 mg ($n = 26$)	20·5	19	12		
	Secukinumab 75 mg ($n = 21$)	19·7	57†	33		
	Secukinumab 150 mg ($n = 27$)	21·3	82§	48†		
	Placebo ($n = 22$)	21·7	9	9		
Rich, 2013[d] (Phase 2)[37]	Secukinumab single ($n = 66$)	19·9	11	5	NR	21/0
	Secukinumab monthly ($n = 138$)	20·8	42§	23†		41/0
	Secukinumab early ($n = 133$)	19·9	55§	37§		34/0·8
	Placebo ($n = 67$)	20·5	2	2		39/1·5

*$P < 0{\cdot}05$; †$P < 0{\cdot}01$; §$P < 0{\cdot}001$ versus placebo or comparator; NR = not reported; NP = nasopharyngitis; URTI = upper respiratory tract infection.

[a]Treatment administered subcutaneously (s.c.) at baseline, weeks 2, 4, 8, 12 and 16. Primary end-point was PASI 75 at week 12. Dermatology Life Quality Index (DLQI) data measured at week 8.[22]

[b]Treatment administered s.c. on day 1 and weeks 1, 2, 4, 6, 8 and 10, with the 280-mg administered monthly. Primary end-point was the % improvement from baseline in PASI score at week 12. DLQI data calculated as the difference in mean values at week 12 relative to baseline.[23]

[c]Secukinumab was administered s.c. at baseline and weeks 4 and 8. One group of 29 patients received a single 25-mg dose at baseline and placebo at weeks 4 and 8. The primary end-point was PASI 75 at week 12. Data from the investigator's global assessment (IGA), which used a more stringent criterion for a score of 1 compared with the PGA used in other trials. Therefore, these IGA data are not directly comparable with PGA data.[36]

[d]Secukinumab 150 mg s.c. was administered at baseline (single), at baseline and weeks 4 and 8 (monthly), or at baseline, weeks 1, 2 and 4 (early). The primary end-point was PASI 75 at week 12. Data from the investigator's global assessment (IGA), which used a more stringent criterion for a score of 1 compared with the PGA used in other trials. Therefore, these IGA data are not directly comparable with PGA data.[37]

a separate group received secukinumab 25 mg at baseline and placebo at weeks 4 and 8.[36] At the two highest dose levels, secukinumab significantly increased PASI 75 response compared with placebo at the week 12 primary end-point (57% and 82% versus 9%; $P = 0{\cdot}002$ and $P < 0{\cdot}001$, respectively). The 150-mg dose also significantly increased PASI 90 and IGA 0/1 rates compared with placebo (52% versus 5%; $P < 0{\cdot}001$, and 48% versus 9%; $P = 0{\cdot}005$, respectively).

In the regimen-finding study, secukinumab 150 mg was administered s.c. at baseline (single dose), baseline and weeks 1, 2 and 4 (early regimen), or baseline and weeks 4 and 8 (monthly regimen).[37] The early and monthly regimens produced significantly higher PASI 75 (55% and 42% versus 2%; $P < 0{\cdot}001$) and IGA 0/1 (37% and 23% versus 2%; $P < 0{\cdot}001$ and $P = 0{\cdot}003$, respectively) rates at week 12 compared with placebo. Patients with PASI 75 responses at week 12 were then re-randomized to maintenance therapy with secukinumab according to a fixed interval (weeks 12 and 24) or at the time when relapse was observed. The fixed-interval strategy group maintained higher PASI 75 and IGA 0/1 rates than the 'retreatment as needed' strategy group during the open-label follow up.

Ixekizumab and brodalumab have also been evaluated in randomized, placebo-controlled phase 2 trials (Table 2). Ixekizumab was administered at doses of 10, 25, 75 or 150 mg s.c. at baseline and weeks 2, 4, 8, 12 and 16, with the primary end-point analysis conducted at week 12.[22] At the three higher doses, ixekizumab significantly increased PASI 75 and physician's global assessment (PGA) 0/1 rates compared with placebo (77–83% versus 8%, and 70–72% versus 8%, respectively; $P < 0{\cdot}001$ for each comparison with placebo). The effects of ixekizumab on PASI were evident by week 1 and maintained through week 20. Immunohistological and gene expression studies revealed broad down-regulation of markers of epidermal pathology and the psoriasis mRNA profile by week 2,[38] consistent with findings for secukinumab in other studies.[21]

Brodalumab was administered at doses 70, 140 or 210 mg s.c. at baseline and weeks 1, 2, 4, 6, 8 and 10, or at 280 mg s.c. at baseline and weeks 4 and 8.[23] At these doses, brodalumab significantly reduced mean PASI scores by 45%, 86%, 86% and 76%, respectively, at the week 12 primary end-point compared with a decrease of 16% for placebo group (all $P < 0{\cdot}001$). The PASI 75 responses were achieved by 77% and 85% of patients treated with the 140-mg and 210-mg doses, respectively. Brodalumab also significantly improved other efficacy measures including PGA 0/1 and Dermatology Life Quality Index ($P < 0{\cdot}01$ at 70 mg, and $P < 0{\cdot}001$ at the other dose levels), and reduced markers of disease pathology including keratin 16 staining in the upper epidermis.

IL-17A in psoriatic arthritis

Psoriatic arthritis affects an estimated 20–30% of psoriasis patients and its onset is, on average, a decade later than cutaneous disease.[39,40] That only a portion of psoriasis patients develop PsA, taken in conjunction with the clinical and immunopathological differences between PsA and RA, suggests that these three immune-mediated diseases share overlapping but distinct pathogenic mechanisms.

Experimental evidence supporting a role of IL-17A in PsA is more limited than in psoriasis or RA. Th17 cells are increased in the circulation of PsA patients, and exhibit a highly differentiated and polyfunctional phenotype suggesting that they play a specific role in the disease.[41] Moreover, IL-17A-producing cells, including Th17 cells and c-Kit-positive mast cells, are increased in the synovial fluid of patients with PsA.[42,43] Synovial fibroblasts isolated from PsA patients, like those from patients with RA, exhibited higher IL-17RA expression compared with cells from patients with osteoarthritis.[42] Moreover, synovial fibroblasts from PsA patients produced higher levels of IL-6, CXCL-8 and matrix metalloproteinase 3 in response to IL-17A compared with cells from osteoarthritis patients – an effect that was blocked by an anti-IL-17RA monoclonal antibody. An intriguing recent observation indicates that mutant Act1, in some cases of PsA, can differentially attenuate TRAF6 versus TRAF2/5 signalling.[14] Taken together, these findings suggest that IL-17A plays a role in PsA pathogenesis.

Clinical findings

In a double-blind, placebo-controlled, proof of concept phase 2 trial, secukinumab was evaluated for treatment of active moderate-to-severe PsA. Patients were randomized to receive secukinumab 10 mg/kg i.v. or placebo at baseline and week 3. The primary end-point, American College of Rheumatology (ACR) 20 response at week 6, was not met (39% versus 23%, $P = 0{\cdot}27$). However, trends for higher ACR20 rates were evident with secukinumab versus placebo at week 12 (39% versus 15%; $P = 0{\cdot}13$) and week 24 (43% versus 18%; $P = 0{\cdot}14$).[44] In general, these ACR20 response rates are lower than rates obtained with TNF inhibitors.[45] In addition to ACR20 responses, good European League Against Rheumatism responses and remission [Disease Activity Score using 28 joint count (DAS28) scores $\leq 2{\cdot}6$] at week 6 occurred more frequently in the secukinumab group (both 22% versus 9%), and significant decreases compared with placebo were seen for Health Assessment Questionnaire–Disability Index (HAQ-DI) ($P = 0{\cdot}002$) and the SF-36 physical component score ($P = 0{\cdot}030$).[44] Secukinumab also produced significant reductions in serum β-defensin-2 concentrations, a potential surrogate marker of psoriatic disease activity. Phase 3 clinical trials in PsA with secu-

kinumab and ixekizumab are ongoing (ClinicalTrials.gov identifiers NCT01392326 and NCT0165239, respectively). The high responses, using an IL-17 pathway inhibitor, in psoriasis compared with modest responses in PsA suggest that IL-17-mediated pathways play a role in both diseases but to different, yet to be defined, extents. Interestingly, a double-blind, placebo-controlled trial of patients with another immune-mediated disease related to PsA, ankylosing spondylitis, yielded favourable results. Patients with active ankylosing spondylitis were treated with two i.v. infusions of 10 mg/kg secukinumab or placebo. At 6 weeks, 14 of 23 (61%) patients receiving secukinumab achieved the primary endpoint of Assessment in SpondyloArthritis international Society (ASAS) 20 response compared with one of six (17%) patients receiving placebo.[46]

IL-17A in rheumatoid arthritis

Experimental evidence

Initial evidence for IL-17A in RA pathogenesis was obtained in rheumatoid synovial explants, which produced functional amounts of IL-17A and exhibited IL-17A-positive cells in T-cell-rich synovial regions.[8] Subsequently, collagen-induced arthritis (CIA) in mice and other animal models of arthritis suggested that IL-17A contributes to immunoinflammatory changes characteristic of RA. Blocking endogenous IL-17A with a soluble murine IL-17 receptor protein suppressed synovial inflammation and joint damage in CIA, whereas IL-17A over-expression by gene transfer or intra-articular injection aggravated these disease characteristics.[4] This study also showed that IL-17A effects were independent of IL-1β, another cytokine known to promote CIA pathology. Consistent with these findings, both inflammatory and destructive features of CIA were markedly suppressed in IL-17A-deficient mice compared with wild-type animals.[5] It was also suggested that IL-17A was crucial for priming collagen-specific T cells and producing collagen-specific antibodies during the sensitization phase of CIA based on these IL-17A-deficient mice. Anti-IL-17A reduced synovial inflammation as well as cartilage and bone damage when administered after the onset of CIA.[6] The reduction in bone damage observed in these studies was associated with fewer osteoclasts and fewer Th17 cells in apposition to the activated osteoclasts, a profile recently observed in rheumatoid synovial tissue.[47]

Staining for IL-17 reveals high levels of IL-17A in the rheumatoid synovium, in the sublining layer and at the margins of lymphocytic aggregates.[48] Elevated levels of IL-17A were detected in serum and synovial fluid of patients with RA,[49–51] and were associated with greater disease activity as reflected by the DAS28 and the presence of anti-citrullinated peptide antibodies in small studies.[50,51] Interleukin-17A mRNA expression in synovial membranes was strongly correlated with markers of inflammation such as elevated peripheral blood C-reactive protein (CRP), was predictive of joint damage progression and showed synergism with TNF expression, particularly in disease of shorter duration.[52] An important but rarely recognized finding in this report was that IL-17 mRNA was expressed in only 15 of 54 patients (28%), in contrast to TNF, which was expressed in all patients. Although 30–40% of subjects in this study had low disease activity, this finding suggests that IL-17 may not be present in all patients with RA.

Interleukin-17A enhances the production of chemokines (e.g., CCL2, CCL20, CXCL-8) and cytokines (e.g. TNF, IL-1β, IL-6) from synovial fibroblasts,[8,53,54] increases production of cartilage-degrading matrix metalloproteinases, blocks new matrix synthesis by chondrocytes[55–57] and stimulates bone resorption by enhancing receptor activator of NF-κB (RANK) ligand expression on osteoblasts and RANK on osteoclast precursors, as well as via increased cytokine production.[58,59] Synergism between IL-17A and TNF has been seen in target cells relevant to RA, including synovial fibroblasts and chondrocytes.[56,60] Both IL-17A and TNF up-regulated production of vascular endothelial growth factor in cultured rheumatoid synovial fibroblasts, which may be important in pannus formation.[61] In total, the effects of IL-17A observed in resident joint cells could promote joint inflammation, cartilage degradation and bone erosion, which is consistent with data from CIA and other experimental arthritis models.[4–6,62,63]

Clinical findings

Early clinical trials suggest that IL-17 pathway inhibitors have some activity in RA. Secukinumab was first assessed in a proof of concept trial in patients with active RA despite stable methotrexate therapy.[21] At a dose of 10 mg/kg i.v. at baseline and week 3, secukinumab significantly improved the area under the treatment response–time curve for ACR20 response ($P = 0{\cdot}011$), adjusted DAS28 score ($P = 0{\cdot}027$), and baseline-adjusted CRP ($P = 0{\cdot}002$) over the 16-week observation period. The activity of secukinumab was evident by week 1 and maintained until the final assessment at week 16. In a subsequent randomized, placebo-controlled, phase 2 trial, secukinumab 75, 150 or 300 mg s.c. monthly produced numerically higher ACR20 response rates compared with placebo at week 16 (47–54% versus 36%), but the differences did not reach statistical significance.[64] However, the secondary end-point of DAS28-CRP score was significantly reduced by secukinumab at the 75-mg and 150-mg doses. At the highest doses, ACR20 response levels were associated with baseline hsCRP levels. Patients with ACR20 responses continued to receive the same dose of secukinumab until week 52, whereas non-responders

received higher doses. The clinical efficacy of secukinumab among responders was maintained through week 52.[65] Responders also had sustained improvements in DAS28-CRP and HAQ-DI. In contrast, patients who did not respond to secukinumab by week 16 derived little benefit from subsequent dose escalation.

Ixekizumab was also evaluated initially in a proof of concept trial, in which patients with active RA despite at least one conventional disease-modifying anti-rheumatic drug (DMARD) received doses of 0·2, 0·6 or 2 mg/kg i.v. or placebo at baseline and weeks 2, 4, 6 and 8.[66] At week 10, the combined ixekizumab group had a significantly greater reduction from baseline in DAS28 compared with the placebo group (–2·3 versus –1·7; $P \leq 0{\cdot}05$), with activity seen by week 1 and maintained until the final assessment at week 16. Ixekizumab was subsequently tested in a phase 2 trial in patients on background DMARD therapy; biologically naive patients received doses of 3–80 mg s.c. and those who were inadequate responders to TNF blockers (TNF-IR) received doses of 80 or 160 mg s.c. at baseline and weeks 1, 2, 4, 6, 8 and 10.[67] Ixekizumab 30 mg produced ACR20 responses in 70% of biologically naive patients at week 12, but the rates ranged from 43 to 54% for the other dose levels (compared with 35% for placebo). Ixekizumab improved ACR20 rates at both dose levels in the TNF-IR patients (39–40% versus 23%; $P < 0{\cdot}05$). Ixekizumab is not being currently developed for RA.

In a randomized, double-blind, dose-escalation phase 1b study in 40 patients with moderate-to-severe RA, brodalumab was administered at doses of 50, 140 or 210 mg s.c. every 2 weeks for six doses or at 420 or 700 mg i.v. every 4 weeks for two doses.[68] At the doses administered, brodalumab was shown to occupy IL-17RA on circulating leucocytes and inhibited IL-17-mediated signalling. While safety was the primary end-point in this trial, ACR20 response was an exploratory end-point and was achieved by 37% of patients treated with brodalumab versus 22% treated with placebo at week 13. In a subsequent randomized, double-blind, placebo-controlled phase 2 trial, brodalumab was administered at doses of 70, 140 or 210 mg s.c. at baseline and weeks 1, 2, 4, 6, 8 and 10 to biologically naive patients with active RA despite methotrexate therapy.[69] ACR50 at week 12, the primary end-point, was achieved in 10–16% of patients in the brodalumab groups and in 13% of patients in the placebo group. Changes in DAS28 also did not differ. Brodalumab is not being explored further in RA.

Potential risks of blocking the Th17–IL-17A pathway

Current therapies for psoriasis, PsA and RA include biological agents that target TNF or other molecules involved in broad immune regulation. Long-term safety experience with these agents is greatest in rheumatology where TNF inhibitors, for example, have been shown to increase the risk of infection (including serious infections) by bacterial pathogens, atypical fungi and opportunistic pathogens.[70] More selective immune inhibition, with less risk, is the rationale underlying development of IL-17 inhibitors. Understanding the normal role of IL-17 in host defence can provide insight into potential risks of IL-17 blockade.

The role of Th17 cells and their effectors in host defence suggests that IL-17A inhibition could increase the risk of serious infection and various immune-mediated disorders. Patients with genetic defects in IL-17RA or IL-17F exhibit chronic mucocutaneous candidiasis, characterized by recurrent or persistent skin, nail and mucosal infections caused by *Candida albicans*, and to a lesser extent by *Staphylococcus aureus*.[71] Cellular responses to IL-17A and IL-17F were abolished in those with IL-17RA deficiency, whereas IL-17F deficiency resulted in impaired, but not abolished, cellular responses. Autoimmune polyendocrine syndrome type 1, caused by mutations in the autoimmune regulator (*AIRE*) gene that normally controls thymic self-tolerance, is associated with autosomal recessive chronic mucocutaneous candidiasis.[72,73] In these patients, the candidiasis appears associated with the presence of autoantibodies against Th17 cytokines including IL-17A, IL-17F and/or IL-22. Patients with autosomal dominant mucocutaneous candidiasis have mutations in the coiled-coil domain of the signal transducer and activator of transcription 1 (*STAT1*) gene, which impairs IL-12 or IL-23 signalling, resulting in defective Th1 and Th17 responses, respectively.[74] Patients with hyper-IgE syndrome caused by an autosomal dominant STAT3 deficiency have a low proportion of IL-17A-producing circulating T cells, and exhibit mucocutaneous infections typically caused by *S. aureus* and *C. albicans*.[75]

So far, safety findings from clinical trials have indicated that IL-17A pathway inhibition results in higher infection rates compared with placebo, (Table 2) but no dominant infection or other safety signal has consistently emerged among this class of biological therapies regardless of indication.

It remains to be seen whether new agents in development such as dual TNF/IL-17A inhibitors are more efficacious in suppressing pathogenic synergy between these cytokines than IL-17A inhibitors alone without conferring increased safety risk.

Insights and conclusions

Phase 2 clinical results with IL-17 inhibitors corroborate experimental data that pointed to the importance of this cytokine in the pathogenesis of multiple immunoinflammatory diseases. A role for IL-17A in psoriasis is based largely on cellular studies rather than animal models, par-

ticularly by the potential of IL-17A to drive innate and adaptive immune responses via keratinocytes and Th17 cells. Much of the experimental evidence for a role for IL-17A in PsA is derived from the experimental evidence in psoriasis and RA. Compared with psoriasis, the experimental evidence base supporting a role for IL-17A in RA pathogenesis, including studies in rheumatoid synovial specimens and animal models, is richer.

Response rates with IL-17 pathway inhibition range from unprecedentedly high in psoriasis, moderate in PsA, to moderate to weak in RA. Pre-clinical evidence for a role of IL-17A in the pathogenesis of psoriasis, PsA and RA are not predictive of this IL-17 inhibitor clinical response rate hierarchy, suggesting that other factors that have yet to be identified might explain the differences in response rates with IL-17 inhibitors across immune-mediated diseases. Supporting this cautionary note are results from a randomized, double-blind, placebo-controlled study of patients with Crohn's disease in which, despite evidence for a role of IL-17A in disease pathogenesis, blockade of IL-17A with secukinumab was ineffective and resulted in higher rates of adverse events compared with placebo.[76] The cellular context in which IL-17 is expressed, the stage or duration of disease, previous therapy, as well as the genetic architecture of the disease in individual patients could be distinguishing factors between psoriasis and synovitis or other inflammatory diseases. There may also be differences in proportions of subjects in these conditions who have IL-17-dependent pathways. The relationship of IL-17 to CRP levels in RA in two independent patient groups, which is not seen in psoriasis, also suggests that the differential interaction of IL-17 and other cell types and cytokines could play an important role in the differential role of IL-17 in disease signs and symptoms. Phase 3 clinical trials with IL-17 inhibitors are ongoing and should provide further information on the role of IL-17A in disease pathogenesis and the promise of these treatments.

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